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(54) **NOVEL 3,3-DIPHENYLPROPYLAMINES, THEIR USE AND PREPARATION**

3,3-DIPHENYLPROPYLAMINE, IHRE VERWENDUNG UND HERSTELLUNG

NOUVELLES 3,3-DIPHENYLPROPYLAMINES, LEUR UTILISATION ET LEUR PREPARATION

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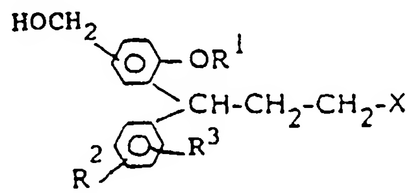
Description

The present invention relates to novel therapeutically active compounds, methods for their preparation, pharmaceutical compositions containing the novel compounds, and the use of the compounds for preparing drugs.

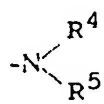
WO 89/06644 discloses 3,3-diphenylpropylamines having anticholinergic activity. In accordance with the present invention novel therapeutically active compounds have now been found, some of which are formed as metabolites in mammals when treated with the 3,3-diphenylpropylamines disclosed in the above-mentioned WO publication. These metabolites have at least as favourable anti-cholinergic properties as the parent compounds and can thus be used for the control of events mediated by acetylcholine, like urination.

The novel compounds of the present invention are represented by the general formula I



I

wherein R^1 signifies hydrogen or methyl, R^2 and R^3 independently signify hydrogen, methyl, methoxy, hydroxy, carbamoyl, sulphamoyl or halogen, and X represents a tertiary amino group of formula II



II

wherein R^4 and R^5 signify non-aromatic hydrocarbyl groups, which may be the same or different and which together contain at least three carbon atoms, preferably at least four carbon atoms, especially at least five carbon atoms, and wherein R^4 and R^5 may form a ring together with the amine nitrogen, said ring having no other heteroatom than the amine nitrogen.

The compounds of formula I can form salts with physiologically acceptable acids, organic and inorganic, and the invention comprises the free bases as well as the salts thereof. Examples of such acid addition salts include the hydrochloride, hydrobromide, hydrogen fumarate, and the like.

When the novel compounds are in the form of optical isomers, the invention comprises the racemic mixture as well as the individual isomers as such.

In the compounds of formula I, R^2 is preferably hydrogen, and R^3 is preferably hydrogen or hydroxy.

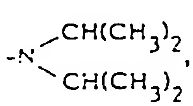
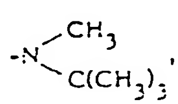
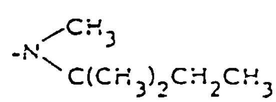
R^2 is preferably in 3-, 4- or 5-position.

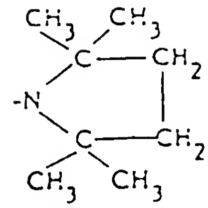
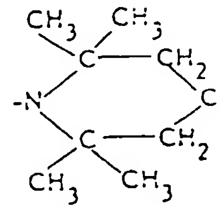
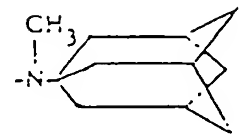
R^3 is preferably in 2-position with respect to the propylamine group.

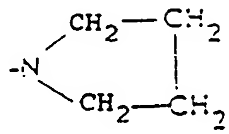
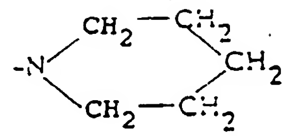
The $HOCH_2$-group is preferably in 5-position.

Preferably, each of R^4 and R^5 independently signifies C_{1-8}-alkyl, especially C_{1-6}-alkyl, or adamantyl, R^4 and R^5 together comprising at least three, preferably at least four carbon atoms. R^4 and R^5 may carry one or more hydroxy groups, and they may be joined to form a ring together with the amine nitrogen atom.

Presently preferred tertiary amino groups X in formula I include the following groups a) - h):

a)  b)  c) 

d)  , e)  , f) 

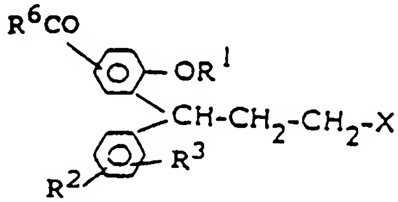
g)  , h) 

Preferably, R^4 and R^5 are both isopropyl.

A presently preferred specific compound of formula I is N,N-diisopropyl-3-(2-hydroxy-5-hydroxymethylphenyl)-3-phenylpropylamine.

The compounds of formula I may, in accordance with the present invention, be prepared by per se conventional methods, and especially by

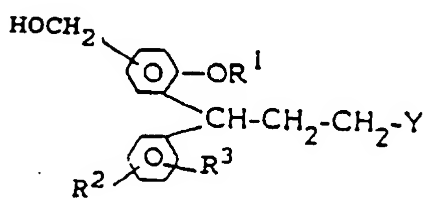
a) reducing the group R^6CO in a 3,3-diphenylpropylamine of formula III



III

wherein R^1 to R^3 and X are as defined above, R^6 is hydrogen or R^7O, where R^7 is hydrogen, (preferably lower) alkyl, alkenyl, alkynyl or aryl (such as phenyl) and any hydroxy groups may be protected, such as by methylation or benzylation, or

b) reacting a reactively esterified 3,3-diphenylpropanol of formula IV



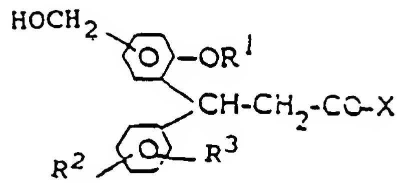
IV

wherein R^1 to R^3 are as defined above and any hydroxy groups may be protected, and wherein Y is a leaving group, preferably halogen or an alkyl or arylsulphonyloxy group, with an amine of formula V

$$H - X \qquad V$$

wherein X is as defined above, or

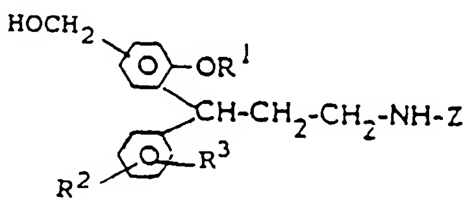
c) reducing a 3,3-diphenylpropionamide of formula VI



VI

wherein R^1 to R^3 and X are as defined above and any hydroxy groups may be protected, preferably using a complex metal hydride, or

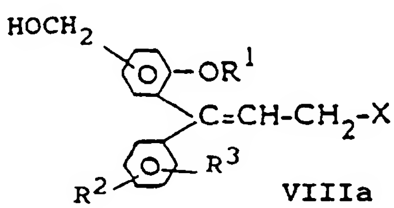
d) N-methylating a secondary 3,3-diphenylpropylamine of formula VII



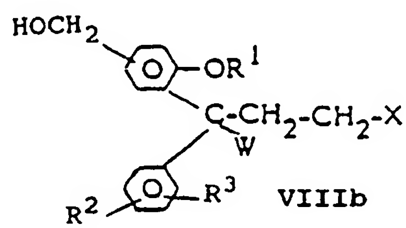
VII

wherein R^1 to R^3 and X are as defined above and any hydroxy groups may be protected, and wherein Z has the same meaning as R^4 and R^5 with the exception of methyl, Z preferably being a hydrocarbyl group comprising at least three carbon atoms, the N-methylation preferably being carried out using formaldehyde or formic acid, or

e) reducing a 3,3-diphenylpropenamine of formula VIIIa or a 3,3-diphenylpropylamine of formula VIIIb



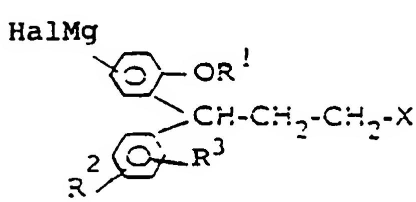
VIIIa



VIIIb

wherein R^1 to R^3 and X are as defined above and any hydroxy groups may be protected, and W signifies a hydroxy group or a halogen atom, preferably by means of catalytic hydrogenation,

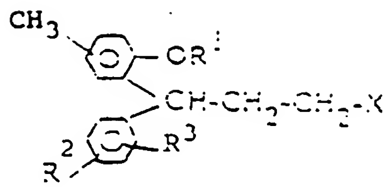
f) reacting a 3,3-diphenylpropylamine of formula IX



IX

wherein R^1 to R^3 and X are as defined above, and Hal is halogen, with formaldehyde or a formaldehyde equivalent (such as s-trioxane), or

g) oxidizing the methyl group of a diphenylpropylamine of formula X



X

wherein R^1 to R^3 and X are as defined above, and

i) when necessary splitting off hydroxy protecting groups in the compounds obtained, if desired after mono- or di-halogenation of one or both of the phenyl rings, and/or
ii) if desired converting the obtained bases of formula I into salts thereof with physiologically acceptable acids, or vice versa, and/or
iii) if desired separating an obtained mixture of optical isomers into the individual enantiomers, and/or
iv) if desired methylating an ortho-hydroxy group in an obtained compound of formula I, wherein R^1 is hydrogen and/or R^3 is hydroxy.

The oxidation in process g) above may be performed chemically, electrochemically or enzymatically. Chemical oxidation is advantageously performed using a metal salt or oxide like ceric ammonium nitrate, manganese oxides, chromium oxides, vanadinium oxides, cobalt acetate, aluminium oxide, bismuth molybdate or combinations thereof. Chemical oxidation may also be effected by peracids, with or without a catalyst, or with halides. Electrochemical oxidation may be conducted with or without a catalyst. For enzymatical oxidation, it is preferred to use bacteria or yeast (e.g. Candida Guilliermondi, Candida Tropical is).

The removal of hydroxy protecting groups according to i) above can e.g. be done by treatment with hydrobromic acid, borontribromide or by catalytic hydrogenation.

The separation of mixtures of optical isomers, according to ii) above, into the individual enantiomers can e.g. be achieved by fractional crystallization of salts with chiral acids or by chromatographic separation on chiral columns.

The starting compounds of formula III and IX may be prepared as described in the preparation example described below. The starting materials used in processes b) to e) and g) may be prepared as described in the afore-mentioned WO 89/06644 (the disclosure of which is incorporated by reference herein) with due consideration of the disclosure in the present preparation example.

In accordance with the present invention, the compounds of formula I, in the form of free bases or salts with physiologically acceptable acids, can be brought into suitable galenic forms, such as compositions for oral use, for injection, for nasal spray administration or the like, in accordance with accepted pharmaceutical procedures. Such pharmaceutical compositions according to the invention comprise an effective amount of the compounds of formula I in association with compatible pharmaceutically acceptable carrier materials, or diluents, as is well known in the art. The carriers may be any inert material, organic or inorganic, suitable for enteral, percutaneous or parenteral administration, such as: water, gelatin, gum arabicum, lactose, microcrystalline cellulose, starch, sodium starch glycolate, calcium hydrogen phosphate, magnesium stearate, talcum, colloidal silicon dioxide, and the like. Such compositions may also contain other pharmaceutically active agents, and conventional additives, such as stabilizers, wetting agents, emulsifiers, flavouring agents, buffers, and the like.

The compositions according to the invention can e.g. be made up in solid or liquid form for oral administration, such as tablets, capsules, powders, syrups, elixirs and the like, in the form of sterile solutions, suspensions or emulsions for parenteral administration, and the like.

The compounds and compositions can, as mentioned above, be used for the same therapeutical indications as the compounds of the above-mentioned WO 89/06644, i.e. for the treatment of acetylcholine-mediated disorders, such as urinary incontinence. The dosage of the specific compound will vary depending on its potency, the mode of administration, the age and weight of the patient and the severity of the condition to be treated. The daily dosage may, for example, range from about 0.01 mg to about 4 mg per kilo of body weight, administered singly or multiply in doses e.g. from about 0,05 mg to about 200 mg each.

The invention will be further illustrated by the following non-limiting example and pharmacological tests. Reference will be made to the accompanying drawing where the only figure (Fig. 1) shows bladder pressure inhibition curves for a compound of the present invention and a prior art compound, respectively.

General

N.M.R data were acquired on a Jeol JNM-EX 270 Fourier transform spectrometer. Spectra were recorded with tetramethylsilane (TMS) as internal standard at 30°C. Infrared spectra were recorded on a Perkin Elmer 599B instrument. Non-corrected melting points were obtained on a Koeffler apparatus. Gas chromatography was performed on a HP 5940 instrument with a 10 m HP-1 column and the oven heated in the linear temperature gradient mode.

EXAMPLE 1

(+)-N,N-Diisopropyl-3-(2-hydroxy-5-hydroxymethylphenyl)-3-phenylpropylamine (+) mandelate, and (-)-N N-diisopropyl-3-(2-hydroxy-5-hvdroxymethylphenyl)-3-phenylpropylamine (-) mandelate

a) 6-Bromo-4-phenyl-3,4-dihydro-coumarine

A solution of p-bromophenol (138 g, 0.8 mole), cinnamic acid (148 g, 1.0 mole), acetic acid (200 g) and conc. sulfuric acid was refluxed for 2 h. Volatile material was distilled at reduced pressure. The residual syrup was cooled and triturated with cold water, giving a semi-crystalline mass. This was washed extensively with water, saturated sodium carbonate and finally with water again. The material was filtered through a sintered glass funnel, and then mixed with an equal weight of ethanol. The slurry was stirred at room temperature for 1 h and then filtered. The resulting product was washed briefly with ethanol and then diisopropyl ether. After drying, 135 g (55.7%) of the title compound was isolated as white crystals, melting at 117°C.

b) Methyl 3-(2-benzyloxy-5-bromophenyl)-3-phenylpropanonate

6-Bromo-4-phenyl-3,4-dihydro-coumarine (290 g, 0.96 mole) was dissolved in a mixture of methanol (1 L) and acetone (1 L). To the above solution were added potassium carbonate (160 g, 1.16 mole), α-chlorotoluene (140 g, 1.1 mole) and sodium iodide (30 g, 0.47 mole), and the mixture was stirred under reflux for 3 h. The solution was concentrated by distillation, and the residue treated with water and extracted with diethyl ether. The ethereal layer was washed with water, saturated sodium carbonate solution and water, successively. The organic layer was dried over sodium sulfate, filtered and then evaporated to give 420 g (≈100%) of the title compound as a light yellow oil.

c) 3-(2-benzyloxy-5-bromophenyl)-3-phenylpropanol

Methyl 3-(2-benzyloxy-5-bromophenyl)-3-phenylpropanonate (112 g, 0.26 mole) was dissolved in tetrahydrofuran (250 mL) and added dropwise under nitrogen atmosphere to a suspension of lithium aluminiumhydride (5.9 g, 0.16 mole) in tetrahydrofuran (250 mL). The mixture was stirred overnight under nitrogen atmosphere. The excess hydride was decomposed by addition of a small amount of HCl (aq, 2 M). The solution was filtered on a pad of Celatom, and the solids were washed thoroughly with ether. The combined ethereal solution was washed with HCl (2 M), water, sodium hydroxide (2 M) and then with water again. The organic solution was dried over sodium sulfate, filtered and evaporated to give 98.5 g (95%) of the title compound as a colourless oil. A small fraction of the oil was crystallized from diisopropyl ether/petroleum ether giving crystals which melted at 70°C.

d) 3-(2-benzyloxy-5-bromophenyl)-3-phenylpropyl-p-toluenesulfonate

To a solution of 3-(2-benzyloxy-5-bromophenyl)-3-phenylpropanol (107 g, 0.24 mole) in dichloromethane (300 mL) and pyridine (75 mL) at 0°C was added p-toluene sulfonylchloride (57 g, 0.3 mole). The solution was stirred at 0°C overnight and then evaporated at reduced pressure and at a bath temperature below 50°C. The remainder was poured onto water and then the mixture was extracted with diethyl ether. The organic layer was washed with water, HCl (2 M) and water successively, and finally dried over sodium sulfate. After filtration the ethereal solution was evaporated at a bath temperature of <50°C giving 137 g (≈100%) of 3-(2-benzyloxy-5-bromophenyl)-3-phenylpropyl-p-toluenesulfonate as a pale yellow oil.

e) N,N-Diisopropyl-3-(2-benzyloxy-5-bromophenyl)-3-phenylpropylamine

3-(2-benzyloxy-5-bromophenyl)-3-phenylpropyl-p-toluenesulfonate (115 g, 0.2 mole) was dissolved in a mixture of acetonitrile (150 g) and diisopropylamine (202 g, 2.0 mole) and the mixture was refluxed for 4 days. The solution was evaporated, and to the resulting syrup was added sodium hydroxide (2 M, 200 mL). The mixture was concentrated, cooled and then extracted with diethyl ether. The ethereal layer was extensively washed with water. The amine was extracted with excess sulfuric acid (1 M). The aqueous layer was washed with diethyl ether and then basified with sodium hydroxide (11 M). The mixture was then extracted with diethyl ether. The organic layer was washed with water, dried over sodium sulfate, filtered and then evaporated to give 78.6 g (78%) of N,N-diisopropyl-3-(2-benzyloxy-5-bromophenyl)-3-phenylpropylamine as a pale yellow oil. The 1-H N.M.R spectrum was in accordance with the above structure.

f) Resolution

To a solution of N,N-diisopropyl-3-(2-benzyloxy-5-bromophenyl)-3-phenylpropylamine (255 g, 0.53 mole) in ethanol (750 g) was added L-(+)-tartaric acid (80 g, 0.53 mole). When all material was dissolved, diethyl ether (90

g) was added and crystallization commenced. After being stored at room temperature overnight, the formed salts were filtered off, washed with fresh ethanol-diethyl ether solution (2:1) and dried to give 98 g of white crystals melting at 156°C. $[\alpha]^{22}$= 16.3° (c = 5.1, ethanol)

The mother liquor from the precipitation with L-(+)-tartaric acid was evaporated. The resulting syrup was treated with sodium hydroxide (2 M) and extracted with diethyl ether. The organic phase was washed with water, dried over sodium sulfate, filtered and then evaporated, giving 170 g of free base. The base (170 g, 0.35 mole) was dissolved in ethanol (500 mL), and D-(-)-tartaric acid (53 g, 0.53 mole) was added. When all had dissolved, diethyl ether (50 mL) was added and crystallization commenced. The crystals were filtered off and washed with fresh ethanol-diethyl ether solution giving 105 g of crystals melting at 154-155°C. $[\alpha]^{22}$ = -16.4° (c = 5.0, methanol)

The mother liquor was concentrated, basified and treated as above, yielding 80 g of free base. This base was dissolved in ethanol, and treated with L-(+)-tartaric acid as described above, yielding additional 20 g of the dextrorotatory form of the salt. (M.p. 156°C).

In an analogous manner, 20 g of the levorotatory form could be obtained.

The pooled dextrorotatory form was dissolved in water and basified with sodium hydroxide (2 M). The mixture was then extracted with diethyl ether. The organic phase was washed with water, dried over sodium sulfate, filtered and finally evaporated to give the chiral amine (88 g) as a colourless oil. $[\alpha]^{22}$ = 16.3° (c = 5.1, ethanol)

In an analogous fashion, the levorotatory base was obtained (90 g). $[\alpha]^{22}$ = -16.1° (c = 4.2, ethanol). The optical purity as assessed by chromatography was >99%.

g1) <u>(+)-N,N-Diisopropyl-3-(2-benzyloxy-5-carboxyphenyl)-3-phenylpropylamine hydrochloride</u>

A mixture of magnesium (12.2 g, 0.5 mole), ethyl bromide (2 g), and iodine (a small crystal) in dry diethyl ether (200 mL) was warmed until the reaction started. (+)-N,N-diisopropyl-3-(2-benzyloxy-5-bromophenyl)-3-phenylpropylamine (45.6 g, 0.095 mole) and ethyl bromide (32.7 g, 0.3 mole) dissolved in dry diethyl ether (250 mL) were then added dropwise under nitrogen atmosphere. The mixture was refluxed for 1.5 h and then cooled in an acetone/dry-ice bath, whereupon powdered dry ice (≈100 g) was added gently. Tetrahydrofuran was added when needed to prevent the mixture from solidification. The reaction mixture was stirred for 0.5 h when ammonium chloride (200 mL, 20% w/w) was added. The mixture was stirred vigorously until two transparent phases were formed, and then filtered through a pad of Celatom. The aqueous layer was washed with diethyl ether and then acidified with hydrochloric acid to pH 1. The precipitated semi-crystalline gum was washed with water, and then transferred to a round bottom flask. The product was dried by co-evaporation with acetone, benzene, toluene, diisopropyl ether and methanol, successively. The title compound (35.1 g, 77%) was isolated as friable shiny flakes and used without any further purification.

g2) <u>(-)-N,N-Diisopropyl-3-(2-benzyloxy-5-carboxyphenyl)-3-phenylpropylamine hydrochloride</u>

This product was isolated in 81 % yield in a corresponding way as described above from (-)-N,N-diisopropyl-3-(2-benzyloxy-5-bromophenyl)-3-phenylpropylamine.

h1) <u>(+)-N,N-Diisopropyl-3-(2-benzyloxy-5-carbomethoxyphenyl-3-phenylpropylamine</u>

(+)-N,N-Diisopropyl-3-(2-benzyloxy-5-carboxyphenyl)-3-phenylpropylamine (34 g, 0.07 mole) was dissolved in methanol (300 mL) containing sulfuric acid (6 g) and refluxed for 6 h. The solution was then cooled and concentrated. To the mixture were added ice-water and a slight excess of saturated sodium carbonate solution. The mixture was then extracted with diethyl ether. The organic phase was washed with water, dried over sodium sulfate, filtered and evaporated, giving 30 g (93%) of crude ester. Recrystallisation from diisopropyl ether gave white crystals melting at 85-86°C. The 1-H N.M.R. spectrum was in accordance with the above structure.

h2) <u>(-)-N,N-diisopropyl-3-(2-benzyloxy-5-carbomethoxyphenyl)-3-phenylpropylamine</u>

The title compound was obtained from (-)-N,N-diisopropyl-3-(2-benzyloxy-5-carboxyphenyl)-3-phenylpropylamine in a similar manner as described above for the dextro isomer in a 93 % yield.

i1) <u>(-)-N,N-Diisopropyl-3-(2-benzyloxy-5-hydroxymethylphenyl)-3-phenylpropylamine</u>

(+)-N,N-Diisopropyl-3-(2-benzyloxy-5-carbomethoxyphenyl)-3-phenylpropylamine (30 g, 0.065 mole) dissolved in diethyl ether (250 mL) was added dropwise under nitrogen to a suspension of lithium aluminiumhydride (1.9 g, 0.05 mole) in dry diethyl ether (150 mL). The mixture was stirred overnight at room temperature, and the excess hydride was decomposed by the addition of water (≈5 g). The mixture was stirred for 10 min, when sodium sulfate (s) was added. After stirring for 20 minutes, the mixture was filtered and then evaporated to give 28.4 g of the title compound as a colourless oil.

i2) <u>(+)-N,N-Diisopropyl-3-(2-benzyloxy-5-hydroxymethylphenyl)-3-phenylpropylamine</u>

The title compound was obtained in an analogous fashion as described above for the levo isomer from (-)-N,N-diisopropyl-3-(2-benzyloxy-5-carbomethoxyphenyl)-3-phenylpropylamine.

j1) <u>(+)-N,N-Diisopropyl-3-(2-hydroxy-5-hydroxymethylphenyl)-3-phenylpropylammonium (+) mandelate</u>

(+)-N,N-Diisopropyl-3-(2-benzyloxy-5-hydroxymethylphenyl)-3-phenylpropylamine (28.2 g, 0.065 mole) was dissolved in methanol (300 g). Raney Nickel (one teaspoon) was added and the mixture was hydrogenated at atmospheric pressure until the theoretical amount of hydrogen was consumed. The progress of the reaction was

monitored by gas chromatography. The mixture was then filtered through a pad of Celatom, and the solvent was removed by evaporation at a bath temperature <50°C. The resulting oil was dissolved in diethyl ether, and the ethereal solution was washed with water, dried over sodium sulfate and evaporated giving 22.2 g of a colourless oil. $[\alpha]^{22}$ = 16.7° (c = 4.9, ethanol).

To the above oil, dissolved in 2-propanol (50 g) was added S-(+)-mandelic acid (9.6 g, 0.06 mole) in 2-propanol (50 g). Dry diethyl ether (50 g) was added, and the solution was left for several hours. The resulting heavy, white crystals were filtered off and washed with a mixture of 2-propanol and diethyl ether (1:1 v/v) and then dried, yielding 25 g of the title compound which melted at 148°C. $[\alpha]^{22}$ = 38.3° (c = 5.1, methanol).

The 1-H N.M.R. spectrum was in accordance with the above structure.

Chiral purity as assessed by H.P.L.C. was >99%.

Elementary Anal. Theor.	C: 73.0	H: 8.0	N: 2.8	O: 16.2
Found	C: 72.9	H: 8.1	N: 3.0	O: 16.5

j2) <u>(-)-N,N-Diisopropyl-3-(2-hydroxy-5-hydroxymethylphenyl)-3-phenylpropylammonium (-) mandelate</u>

The title compound was obtained from (-)-N,N-diisopropyl-3-(2-benzyloxy-5-hydroxymethylphenyl)-3-phenylpropylamine in an analogous manner to that described in j1) above.

Elementary Anal. Theor.	C: 73.0	H: 8.0	N: 2.8	O: 16.2
Found	C: 73.2	H: 8.1	N: 3.0	O: 16.5

The free base had an optical rotation of $[\alpha]^{22}$ = -15.5° (c = 5.0, ethanol).

The 1-(-)-mandelic acid salt had a m.p. of 147-148°C and an optical rotation $[\alpha]^{22}$ = -37.9° (c = 4.7, methanol).

The optical purity as assessed by H.P.L.C. was >99 %.

<u>Pharmacology</u>

Pharmacological tests performed with one compound of the invention and three prior art compounds disclosed in the above mentioned WO 89/06644 will now be described. The following compounds were used:

(A) (+)N,N-diisopropyl-3-(2-hydroxy-5-methylphenyl)-3-phenylpropylamine, hydrochloride (WO 89/06644);
(B) N,N-diisopropyl-3-bis-(2-hydroxyphenyl)propylamine hydrochloride (WO 89/06644);
(C) (+)N,N-diisopropyl-3-(5-chloro-2-hydroxyphenyl)-3-(2-hydroxyphenylpropylamine, hydrochloride (WO 89/06644);
(D) N,N-diisopropyl-3-(2-hydroxy-5-hydroxymethylphenyl)-3-phenylpropylamine (-) mandelic acid salt (Example 1 above).

Raised index numerals in the text below refer to literature references listed at the end of the description.

<u>Muscarinic Receptor Binding Studies</u>

The tissue preparations and the general methods used have been described in detail elsewhere for the parotid gland[1], urinary bladder[2], heart[3] and cerebral cortex[3], respectively. Male guinea pigs (250-400 g body weight) were killed by a blow on the neck and exsanguinated. The brain was placed on ice for dissection of the cerebral cortex (grey matter only). Urinary bladders, hearts and parotid glands were dissected in a Krebs-Henseleit buffer (pH 7.4) containing 1 mM phenyl methyl sulfonyl fluoride (PMSF, a protease inhibitor). Dissected tissues were homogenized in an ice-cold sodium-potassium phosphate buffer (50 mM, pH 7.4) containing 1 mM PMSF, using a Polytron PT-10 instrument (bladder, heart, parotid) and a Potter-Elvehjem Teflon homogenizer (cortex). All homogenates were finally diluted with the ice-cold phosphate/PMSF buffer to a final protein concentration of ≤ 0.3 mg/ml and immediately used in the receptor binding assays. Protein was determined by the method of Lowry et al. (1951)[4], using bovine serum albumin as the standard.

The muscarinic receptor affinities of the unlabelled compounds <u>A</u> to <u>D</u> identified above were derived from competition experiments in which the ability to inhibit the receptor specific binding of (-)^{3}H-QNB (1-quinuclidinyl[phenyl-4-3H] benzilate, 32.9 Ci/mmole) was monitored as previously described[3,5]. Each sample contained 10 µl of (-)^{3}H-QNB (final concentration 2 nM), 10 µl solution of test compound and 1.0 ml tissue homogenate. Triplicate samples were incubated under conditions of equilibrium, i.e., at 25°C for 60 minutes (urinary bladder), 80 minutes (heart and cerebral cortex)

or 210 minutes (parotid gland), respectively. Non-specific binding was determined in the presence of 10 μM unlabelled atropine. Incubations were terminated by centrifugation[2], and the radioactivity in the pellets was determined by liquid scintillation spectrometry[2].

IC_{50}-values (concentration of unlabelled compound producing 50% inhibition of the receptor specific (-)^{3}H-QNB binding) were graphically determined from the experimental concentration-inhibition curves. Affinities, expressed as the dissociation constants K_i, were calculated by correcting the IC_{50} for the radioligand-induced parallel shift and differences in receptor concentration, using the method of Jacobs et al. (1975)[6]. The binding parameters for (-)^{3}H-QNB (K_D and receptor densities) used in these calculations were determined in separate series of experiments[1-3]. The K_i values obtained for bladder, heart, parotid and cortex, respectively, are presented in Table 1 below.

Functional in vitro studies

Male guinea pigs, weighing about 300 g, were killed by a blow on the neck and exsanguinated. Smooth muscle strips of the urinary bladder were dissected in a Krebs-Henseleit solution (pH 7.4). The strip preparations were vertically mounted between two hooks in thermostatically controlled (37°C) organ baths (5 ml). One of the hooks was adjustable and connected to a force transducer (FT 03, Grass Instruments). The Krebs-Henseleit solution was continuously bubbled with carbogen gas (93.5% O_2/6.5% CO_2) to maintain the pH at 7.4. Isometric tension was recorded by a Grass Polygraph (Model 79D). A resting tension of approximately 5 mN was initially applied on each muscle strip and the preparations were allowed to stabilize for at least 45 min. The resting tension was repeatedly adjusted and the preparations were washed several times during the stabilization period.

Carbachol (carbamylcholine chloride) was used as the standard agonist. In each experiment, the viability of the preparations and the reproducibility of their contractile responses were initially tested by three consecutive additions of a submaximal concentration (3 x 10^{-6} M) of carbachol. A complete concentration-response curve to carbachol was then generated by cumulative addition of carbachol to the organ-bath (i.e., stepwise increase of the agonist concentration until the maximal contractile response was reached), followed by washing out and a resting period of at least 15 min. before a fix concentration of the test compound (antagonist) was added to the organ-bath. After 60 min. of incubation with the antagonist, a second cumulative concentration-response curve to carbachol was generated. Responses were expressed as per cent of the maximal response to carbachol. EC_{50}-values for carbachol in the absence (control) and presence of antagonist were graphically derived and dose ratios (r) were calculated. Dissociation constants, K_B, for the antagonists were calculated using equation (1)[7], where [A] is the concentration of test compound.

$$K_B = [A]/r\text{-}1 \qquad (1)$$

The K_B values obtained for compounds A, B and D identified above are shown in Table 1 below.

Table 1

Test compound	K_B nm bladder	K_i nM bladder	K_i nM heart	K_i nM parotid	K_i nM cortex
(A)	3.0	2.7	1.6	4.8	0.8
(B)		10.2	6.7	2.6	1.5
(C)	2.6	2.5	0.9	2.7	0.4
(D)	4.1	4.5	0.9	4.7	0.7

Functional in vivo studies

a) Animal preparation

Adult cats were anaesthetized with mebumal (42 mg/kg) intraperitoneally. When the animal was asleep, an infusion cannula was inserted into the foreleg vein and the cat was given alpha-chloralose. During the experiment the animal was placed on an operation table warmed up with a feedback controlled electric pad. The cat was tracheotomized. For blood pressure registration, a polyethylene catheter was inserted into the femoral artery, with the tip in aorta, and connected via a three-way stopcock to a blood pressure transducer and a Grass polygraph. Heart rate was registered by connecting a tachograph to a driver amplifier which received the signal from the blood pressure transducer. Blood flow in the central mesenteric artery was measured by an ultrasound flow probe around the artery connected to a transonic blood flow meter and then to a Grass polygraph for registration of the flow. For infusion of the test substances, compounds D and A (as identified above), a polyethylene catheter was inserted into the femoral vein three-way stopcock to a syringe placed in an infusion pump (Sage instrument).

Through an incision in the proximal urethra, a catheter was inserted into the urinary bladder. At the beginning of each experiment, this catheter was connected to an open vessel, which was filled with 38°C tempered physiological saline and placed above the animal. During this stabilization period the bladder relaxed, leading to a filling of the bladder with saline, under constant hydrostatic pressure. After the stabilization period, the bladder catheter was connected to a pressure transducer, for registration of intravesical pressure. Blood pressure, heart rate, blood flow and bladder pressure were recorded simultaneously and continuously throughout the experiment. The animals were left for at least 45 minutes to achieve steady state in cardiovascular variables before starting the experiment.

Bladder pressure was measured at 8 minutes after the end of infusion of the test substance. The surgical preparation was tested by intravenous injection of 0.25 μg/kg b.w. of noradrenalin and 0.5 μg/kg b.w. of acetylcholine.

b) Dosing

To study the dose-response relationship of compound D identified above, the substance was administered at the doses 0.000 (physiological saline), 0.003, 0.010, 0.030 and 0.100 mg/kg, respectively, with infusion during 2 minutes and an infusion volume of 1 mL/kg. Every cat got all doses and was left to reestablish at least 45 minutes between the 0.003 and 0.010 mg/kg doses, and 60 minutes between the 0.030 and 0.100 mg/kg doses.

c) Statistical methods and calculation

The results are presented in absolute values and calculated as mean value ± standard deviation

d) Results

(i) Blood pressure

In general, intravenous administration of compound D had little or no effect on the blood pressure except at dose of 0,3 mg/kg. This dose caused an increase with 10% and with 6 % for diastolic blood pressure and systolic blood pressure, respectively.

(ii) Blood flow

Intravenous administration of compound D caused an increase with 8, 17 and 21 % of the blood flow in superior mesenterica artery at 0.003, 0.01, and 0.03 mg/kg, respectively. Again at the highest dose (0.3 mg/kg) a 10% increase in blood flow was observed.

(iii) Heart rate

Intravenous administration of compound D caused a decrease with 9 % at the highest dose (0.3 mg/kg).

(iv) Bladder pressure

As appears from Fig. 1, compound D of the present invention produced a dose-dependent inhibition of the acetylcholine-induced effect on the bladder which was about ten times more efficient than that of prior art compound A.

References

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5. Nilvebrant, L.; Sparf, B. Differences between binding affinities of some antimuscarinic drugs in the parotid gland and those in the urinary bladder and ileum. Acta Pharmacol. et Toxicol. 1983 b, 53, 304-313.
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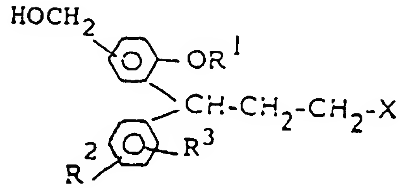
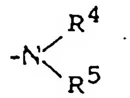
Claims

1. 3,3-Diphenylpropylamines of formula I



I

wherein R^1 signifies hydrogen or methyl, R^2 and R^3 independently signify hydrogen, methyl, methoxy, hydroxy, carbamoyl, sulphamoyl or halogen, and X represents a tertiary amino group of formula II



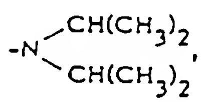
II

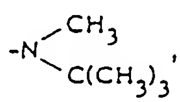
wherein each of R^4 and R^5 independently signify non-aromatic hydrocarbyl groups, which may carry one or more hydroxy groups and which together contain at least three carbon atoms, and wherein R^4 and R^5 may be joined to form a ring having no other heteroatom than the amine nitrogen, their salts with physiologically acceptable acids and, when the compounds can be in the form of optical isomers, the racemic mixture and the individual enantiomers.

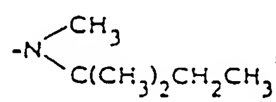
2. 3,3-Diphenylpropylamines according to claim 1, wherein each of R^4 and R^5 independently signifies a saturated hydrocarbyl group, especially saturated aliphatic hydrocarbyl groups such as C_{1-8}-alkyl, especially C_{1-6}-alkyl, or adamantyl, R^4 and R^5 together comprising at least three, preferably at least four carbon atoms.

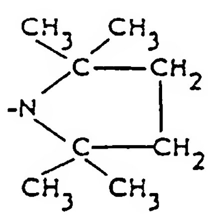
3. 3,3-Diphenylpropylamines according to claim 1 or 2, wherein at least one of R^4 and R^5 comprises a branched carbon chain.

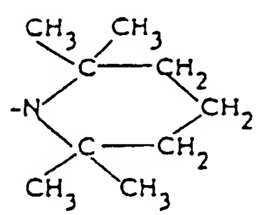
4. 3,3-Diphenylpropylamines according to any one of claims 1 to 3, wherein X signifies any of the following groups a) to h):

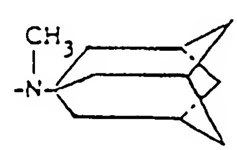
a)  ,

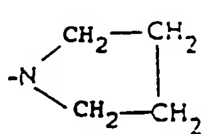
b)  ,

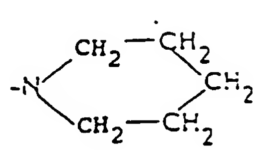
c)  ,

d)  ,

e)  ,

f) 

g)  ,

h) 

5. 3,3-Diphenylpropylamines according to any one of claims 1 to 4, wherein the $HOCH_2$-group is in 5-position, R^2 is hydrogen and R^3 is hydrogen or hydroxy, preferably in 2-position.

6. 3,3-Diphenylpropylamines according to claim 1, selected from N,N-diisopropyl-3-(2-hydroxy-5-hydroxymethylphenyl)-3-phenylpropylamine, its salts with physiologically acceptable acids, racemates and individual enantiomers thereof.

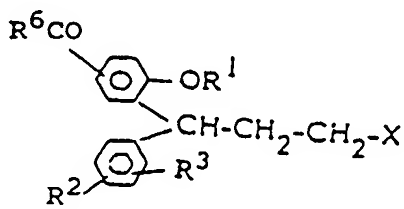
7. 3,3-Diphenylpropylamines according to any one of claims 1 to 6 for use as pharmaceutically active substances, especially as anticholinergic agents.

8. A pharmaceutical composition comprising a 3,3-diphenylpropylamine according to any one of claims 1 to 6 and preferably a compatible pharmaceutical carrier.

9. Use of a 3,3-diphenylpropylamine according to any one of claims 1 to 6 for preparing an anticholinergic drug.

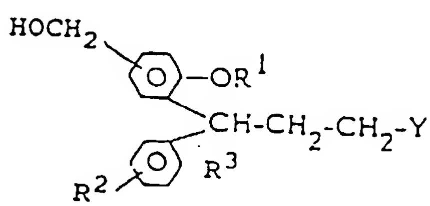
10. A method for preparing 3,3-diphenylpropylamines according to any one of claims 1 to 6, comprising:

a) reducing the group R^6CO of a 3,3-diphenylpropylamine of formula III



III

wherein R^1 to R^3 and X are as defined above, R^6 is hydrogen or R^7O, where R^7 is hydrogen, alkyl, alkenyl, alkynyl or aryl, and any hydroxy groups may be protected, such as by methylation or benzylation, or
b) reacting a reactively esterified 3,3-diphenylpropanol of formula IV

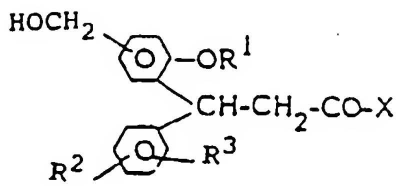


IV

wherein R^1 to R^3 are as defined above, any hydroxy groups may be protected, and wherein Y is a leaving group, with an amine of formula V

$$H-X \qquad V$$

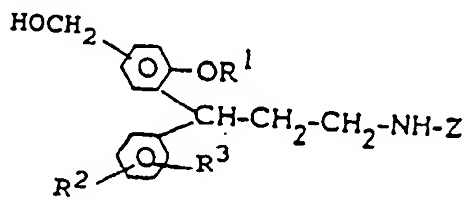
wherein X is as defined above, or
c) reducing a 3,3-diphenylpropionamide of formula VI



VI

wherein R^1 to R^3 and X are as defined above and any hydroxy groups may be protected, or

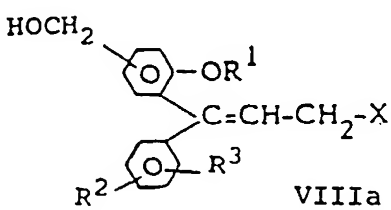
d) N-methylating a secondary 3,3-diphenylpropylamine of formula VII



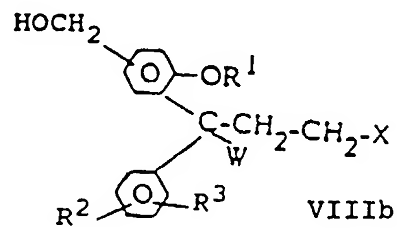
VII

wherein R^1 to R^3 and X are as defined above and any hydroxy groups may be protected, and wherein Z has the same meaning as R^4 and R^5 with the exception of methyl, or

e) reducing a 3,3-diphenylpropenamine of formula VIIIa or a 3,3-diphenylpropylamine of formula VIIIb



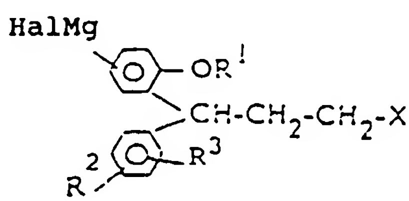
VIIIa



VIIIb

wherein R^1 to R^3 and X are as defined above and any hydroxy groups may be protected, and W signifies a hydroxy group or a halogen atom, or

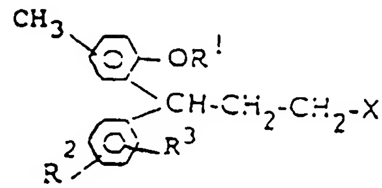
f) reacting a diphenylpropylamine of formula IX



IX

wherein R^1 to R^3 and X are as defined above, and Hal is halogen, with formaldehyde or a formaldehyde equivalent, or

g) oxidizing the methyl group of a diphenylpropylamine of formula X



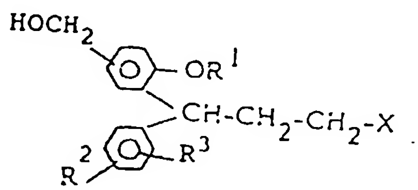
X

wherein R^1 to R^3 and X are as defined above, and

i) when necessary splitting off hydroxy protecting groups in the compounds obtained, if desired after mono- or di-halogenation of one or both of the phenyl rings, and/or
ii) if desired converting the obtained bases of formula I into salts thereof with physiologically acceptable acids, or vice versa, and/or
iii) if desired separating an obtained mixture of optical isomers into the individual enantiomers, and/or
iv) if desired methylating an ortho-hydroxy group in an obtained compound of formula I, wherein R^1 is hydrogen and/or R^3 is hydroxy.

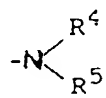
Patentansprüche

1. 3,3-Diphenylpropylamine der Formel I



I

worin R^1 für Wasserstoff oder Methyl steht, R^2 und R^3 unabhängig voneinander für Wasserstoff, Methyl, Methoxy, Hydroxy, Carbamoyl, Sulfamoyl oder Halogen stehen und X für eine tertiäre Aminogruppe der Formel II



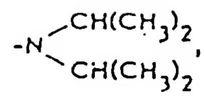
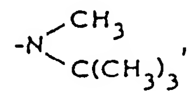
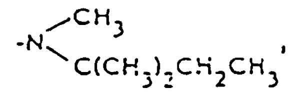
II

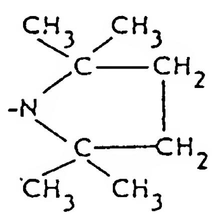
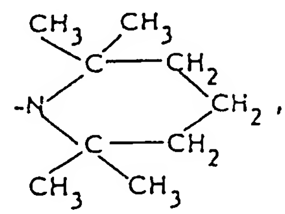
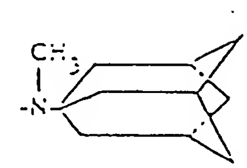
steht, in der jedes R^4 und R^5 unabhängig voneinander für nichtaromatische Kohlenwasserstoffgruppen steht, die eine oder mehrere Hydroxygruppen tragen können und die zusammen wenigstens drei Kohlenstoffatome enthalten und in der R^4 und R^5 miteinander verbunden sein können, um einen Ring zu bilden, der kein anderes Heteroatom besitzt als den Aminstickstoff, ihre Salze mit physiologisch annehmbaren Säuren und, wenn die Verbindungen in Form optischer Isomerer vorliegen können, die racemischen Gemische und die individuellen Enantiomere.

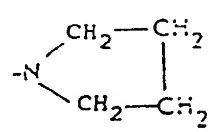
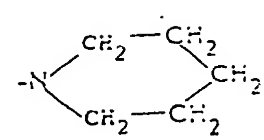
2. 3,3-Diphenylpropylamine nach Anspruch 1, dadurch **gekennzeichnet**, daß jedes R^4 und R^5 unabhängig voneinander eine gesättigte Kohlenwasserstoffgruppe, insbesondere eine gesättigte aliphatische Kohlenwasserstoffgruppe, wie C_{1-8}-Alkyl, insbesondere C_{1-6}-Alkyl, oder Adamantyl bedeutet und R^4 und R^5 zusammen wenigstens drei, vorzugsweise wenigstens vier Kohlenstoffatome umfassen.

3. 3,3-Diphenylpropylamine nach Anspruch 1 oder 2, dadurch **gekennzeichnet**, daß wenigstens ein Rest aus der Gruppe R^4 und R^5 eine verzweigte Kohlenstoffkette umfaßt.

4. 3,3-Diphenylpropylamine nach einem der Ansprüche 1 bis 3, dadurch **gekennzeichnet**, daß X für eine der folgenden Gruppen a) bis h) steht:

a)  b)  c) 

d)  e)  f) 

g)  h) 

5. 3,3-Diphenylpropylamine nach einem der Ansprüche 1 bis 4, dadurch **gekennzeichnet**, daß die $HOCH_2$-Gruppe in der 5-Position ist, R^2 Wasserstoff und R^3 Wasserstoff oder Hydroxy, vorzugsweise in der 2-Position, ist.

6. 3,3-Diphenylpropylamine nach Anspruch 1, ausgewählt aus N,N-Diisopropyl-3-(2-hydroxy-5-hydroxymethylphenyl)-3-phenylpropylamin, seinen Salzen mit physiologisch annehmbaren Säuren, Racemate und individuellen Enantiomere davon.

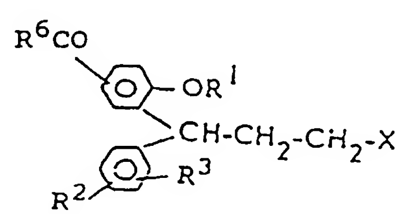
7. 3,3-Diphenylpropylamine nach einem der Ansprüche 1 bis 6 zur Verwendung als pharmazeutisch aktive Substanzen, insbesondere als anticholinerge Mittel.

8. Pharmazeutisches Mittel, umfassend ein 3,3-Diphenylpropylamin nach einem der Ansprüche 1 bis 6 und vorzugsweise einen kompatiblen pharmazeutischen Träger.

9. Verwendung eines 3,3-Diphenylpropylamins nach einem der Ansprüche 1 bis 6 zur Herstellung eines anticholinergen Medikaments.

10. Verfahren zur Herstellung von 3,3-Diphenylpropylaminen nach einem der Ansprüche 1 bis 6, umfassend die folgenden Stufen:

a) Reduktion der R^6CO-Gruppe eines 3,3-Diphenylpropylamins der Formel III

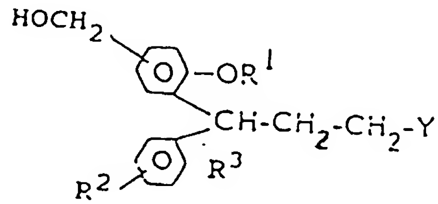


III

in der R^1 bis R^3 und X die oben definierten Bedeutungen haben, R^1 Wasserstoff oder R^7O ist, wobei R^1 Wasserstoff, Alkyl, Alkenyl, Alkinyl oder Aryl ist, und jegliche Hydroxygruppen z.B. durch Methylierung oder

Benzylierung geschützt sein können oder

b) Umsetzung eines reaktiv veresterten 3,3-Diphenylpropanols der Formel IV



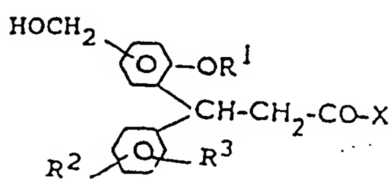
IV

in der R^1 bis R^3 die oben definierten Bedeutungen haben, jegliche Hydroxygruppen geschützt sein können und in der Y eine Austrittsgruppe ist, mit einem Amin der Formel V

$$H-X \qquad V,$$

in der X die oben definierte Bedeutung hat oder

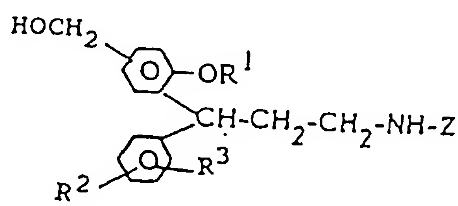
c) Reduktion eines 3,3-Diphenylpropionamids der Formel VI



VI

in der R^1 bis R^3 und X die oben definierten Bedeutungen haben und jegliche Hydroxygruppen geschützt sein können, oder

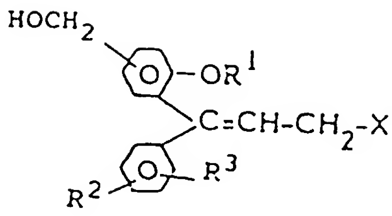
d) N-Methylierung eines sekundären 3,3-Diphenylpropylamins der Formel VII



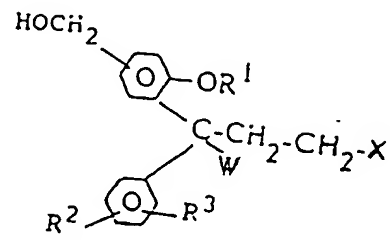
VII

in der R^1 bis R^3 und X die oben definierten Bedeutungen haben, und jegliche Hydroxygruppen geschützt sein können und in der Z die gleiche Bedeutung wie R^4 und R^5 mit Ausnahme von Methyl hat oder

e) Umsetzung eines 3,3-Diphenylpropenamins der Formel VIIIa oder eines 3,3-Diphenylpropylamins der Formel VIIIb



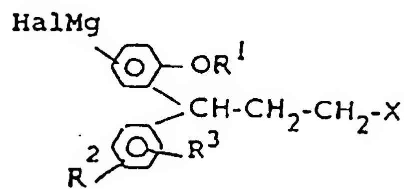
VIIIa



VIIIb

worin R^1 bis R^3 und X die oben definierten Bedeutungen haben und jegliche Hydroxygruppen geschützt sein können und W für eine Hydroxygruppe oder ein Halogenatom steht oder

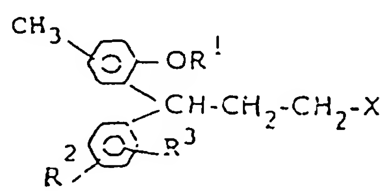
f) Umsetzung eines Diphenylpropylamins der Formel IX



IX

in der R^1 bis R^3 und X die oben definierten Bedeutungen haben und Hal für Halogen steht, mit Formaldehyd oder einem Formaldehyd-Äquivalent oder

g) Oxidation der Methylgruppe eines Diphenylpropylamins der Formel X



X

in der R^1 bis R^3 und X die oben definierten Bedeutungen haben und

i) falls nötig, Abspaltung der Hydroxyschutzgruppen in den erhaltenen Verbindungen, falls erwünscht nach Mono- oder Dihalogenierung eines oder beider Phenylringe und/oder

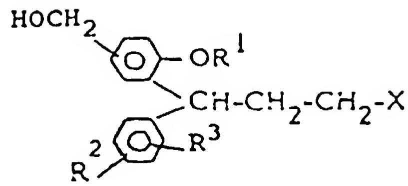
ii) falls gewünscht, Umwandlung der erhaltenen Basen der Formel I in die Salze davon mit physiologisch annehmbaren Säuren oder umgekehrt, und/oder

iii) falls gewünscht, Trennung eines erhaltenen Gemisches optischer Isomere in die individuellen Enantiomeren, und/oder

iv) falls gewünscht, Methylierung einer ortho-Hydroxygruppe in einer erhaltenen Verbindung der Formel I, in der R^1 für Wasserstoff und/oder R^3 für Hydroxy steht.

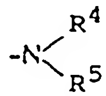
Revendications

1. 3,3-diphénylpropylamines de formule I



I

dans laquelle R^1 représente l'hydrogène ou un groupe méthyle, R^2 et R^3 représentent indépendamment l'hydrogène, un groupe méthyle, méthoxy, hydroxy, carbamoyle, sulfamoyle ou halogéno, et X représente un groupe amino tertiaire de formule II



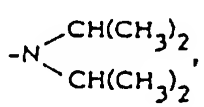
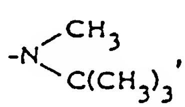
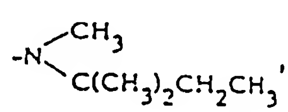
II

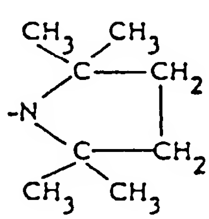
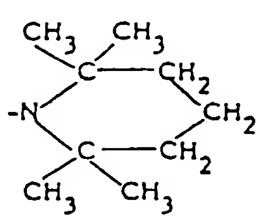
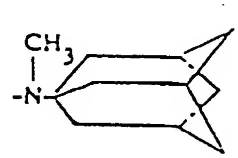
dans laquelle chacun des groupes R^4 et R^5 représente indépendamment un groupe hydrocarbyle non aromatique, qui peut porter un ou plusieurs groupes hydroxy, les groupes R^4 et R^5, conjointement, contenant au moins trois atomes de carbone, et dans laquelle R^4 et R^5 peuvent être joints en formant un noyau n'ayant aucun autre hétéroatome que l'atome d'azote d'amine, leurs sels formés avec des acides physiologiquement acceptables et, lorsque les composés peuvent être sous forme d'isomères optiques, le mélange racémique et les énantiomères distincts.

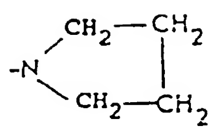
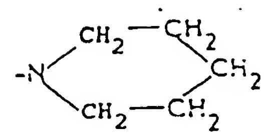
2. 3,3-diphénylpropylamines suivant la revendication 1, dans lesquelles chacun des groupes R^4 et R^5 représente indépendamment un groupe hydrocarbyle saturé, notamment un groupe hydrocarbyle aliphatique saturé tel qu'un groupe alkyle en C_1 à C_8, notamment alkyle en C_1 à C_6 ou un groupe adamantyle, les groupes R^4 et R^5, conjointement, comprenant au moins trois, de préférence au moins quatre atomes de carbone.

3. 3,3-diphénylpropylamines suivant la revendication 1 ou 2, dans lesquelles au moins un des groupes R^4 et R^5 comprend une chaîne carbonée ramifiée.

4. 3,3-diphénylpropylamines suivant l'une quelconque des revendications 1 à 3, dans lesquelles X représente l'un quelconque des groupes a) à h) suivants :

a)  , b)  , c)  ,

d)  , e)  , f) 

g)  , h) 

5. 3,3-diphénylpropylamines suivant l'une quelconque des revendications 1 à 4, dans lesquelles le groupe $HOCH_2$ est en position 5, R^2 représente l'hydrogène et R^3 représente l'hydrogène ou un groupe hydroxy, de préférence en position 2.

6. 3,3-diphénylpropylamines suivant la revendication 1, choisies entre la N,N-diisopropyl-3-(2-hydroxy-5-hydroxyméthylphényl)-3-phénylpropylamine, ses sels formés avec des acides physiologiquement acceptables, ses racémates et les énantiomères distincts correspondants.

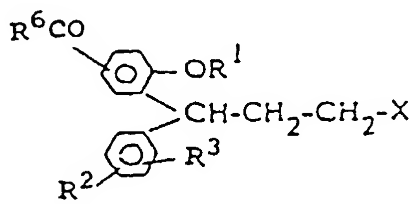
7. 3,3-diphénylpropylamines suivant l'une quelconque des revendications 1 à 6, destinées à être utilisées comme substances pharmaceutiquement actives, notamment comme agents anticholinergiques.

8. Composition pharmaceutique comprenant une 3,3-diphénylpropylamine suivant l'une quelconque des revendications 1 à 6 et, de préférence, un support pharmaceutiquement compatible.

9. Utilisation d'une 3,3-diphénylpropylamine suivant l'une quelconque des revendications 1 à 6 pour la préparation d'un médicament anticholinergique.

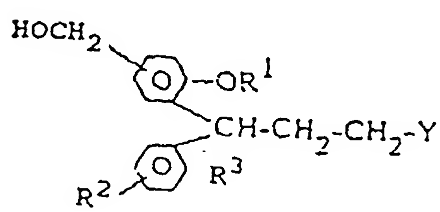
10. Procédé pour la préparation de 3,3-diphénylpropylamines suivant l'une quelconque des revendications 1 à 6, comprenant :

a) la réduction du groupe R^6CO d'une 3,3-diphénylpropylamine de formule III



III

dans laquelle R^1 à R^3 et X répondent aux définitions précitées, R^6 représente l'hydrogène ou un groupe R^7O, dans lequel R^7 représente l'hydrogène, un groupe alkyle, alcényle, alcynyle ou aryle, et n'importe quels groupes hydroxy peuvent être protégés, par exemple par méthylation ou benzylation, ou
b) la réaction d'un 3,3-diphénylpropanol, estérifié réactivement, de formule IV



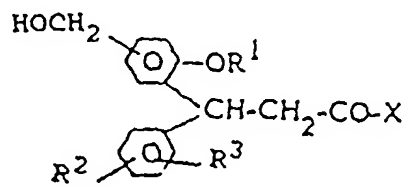
IV

dans laquelle R^1 à R^3 répondent aux définitions précitées, n'importe quels groupes hydroxy pouvant être protégés, et dans laquelle Y représente un groupe partant, avec une amine de formule V

H - X V

dans laquelle X répond à la définition précitée, ou

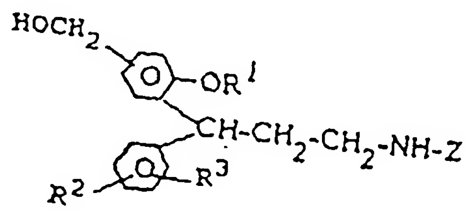
c) la réduction d'un 3,3-diphénylpropionamide de formule VI



VI

dans laquelle R^1 à R^3 et X répondent aux définitions précitées et n'importe quels groupes hydroxy peuvent être protégés, ou

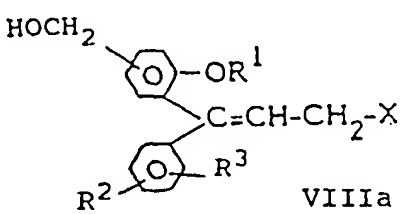
d) la N-méthylation d'une 3,3-diphénylpropylamine secondaire de formule VII



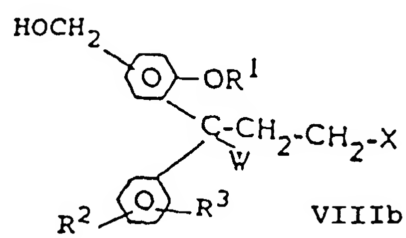
VII

dans laquelle R^1 à R^3 et X répondent aux définitions précitées et n'importe quels groupes hydroxy peuvent être protégés, et dans laquelle Z répond à la même définition que R^4 et R^5 à l'exception du groupe méthyle, ou

e) la réduction d'une 3,3-diphénylpropène-amine de formule VIIIa ou d'une 3,3-diphénylpropylamine de formule VIIIb



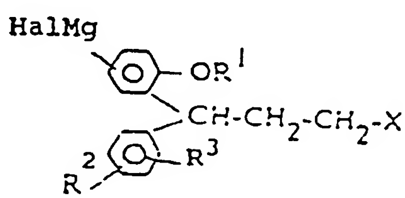
VIIIa



VIIIb

dans laquelle R^1 à R^3 et X répondent aux définitions précitées et n'importe quels groupes hydroxy peuvent être protégés, et W représente un groupe hydroxy ou un atome d'halogène, ou

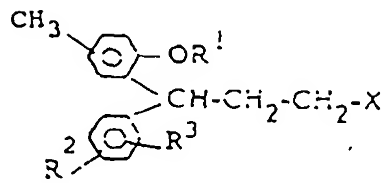
f) la réaction d'une diphénylpropylamine de formule IX



IX

dans laquelle R^1 à R^3 et X répondent aux définitions précitées, et Hal représente un halogène, avec le formaldéhyde ou un équivalent de formaldéhyde, ou

g) l'oxydation du groupe méthyle d'une diphénylpropylamine de formule X



X

dans laquelle R^1 à R^3 et X répondent aux définitions précitées, et

i) lorsque cela est nécessaire, la scission des groupes protecteurs de la fonction hydroxy dans les composés obtenus, si besoin après mono- ou dihalogénation d'un des ou des deux noyaux phényle, et/ou
ii) si cela est désiré, la transformation des bases obtenues de formule I en leurs sels formés avec des acides physiologiquement acceptables, ou vice versa, et/ou
iii) si cela est désiré, la séparation d'un mélange obtenu d'isomères optiques en les énantiomères distincts, et/ou
iv) si cela est désiré, la méthylation d'un groupe ortho-hydroxy dans un composé obtenu de formule I, dans laquelle R^1 représente l'hydrogène et/ou R^3 représente un groupe hydroxy.

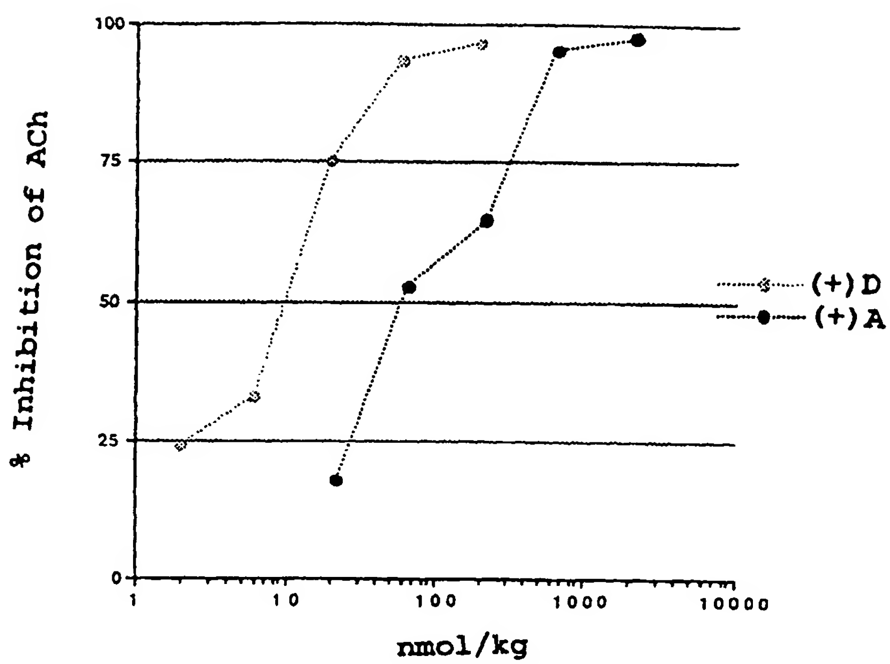


FIG. 1